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Understanding omicron

Studies are beginning to shed light on why omicron behaves so differently to other coronavirus variants, reports **Michael Le Page**

THE global number of confirmed covid-19 cases is currently hitting record levels as omicron spreads. But while this variant – which has around 50 mutations compared with the original SARS-CoV-2 virus – is much more infectious than previous ones, there is growing evidence that it is less likely to cause severe disease in those it infects. Preliminary studies are now providing insights into why this might be the case.

Data from South Africa, the first nation to have an omicron wave, gives an indication of the variant's lower severity. Reported cases there peaked at 117 per cent of the level of the country's delta wave, whereas hospitalisations peaked at 63 per cent and deaths at 24 per cent.

One factor in why omicron seems to be sending a lower proportion of cases to hospital could be that more people are now protected against severe disease, due to previous infections and vaccination. However, animal studies suggest that omicron is also inherently less likely to cause severe symptoms.

For instance, a team led by James Stewart at the University of Liverpool, UK, has found that mice become less ill and recover faster with omicron compared with other variants. "Ours is one of a number of animal studies now," says Stewart. "They do point to very much the same thing."

Work by Joe Grove at the University of Glasgow, UK, and his colleagues suggests that the reason omicron is less severe is that it infects cells in a slightly different way. The process begins when the spike protein of the virus binds to a protein called ACE2 that protrudes from the surface of most human cells.

The second step occurs when the spike protein is cut by another



WALDO SWIEGERS/BLOOMBERG VIA GETTY IMAGES

Inspecting samples at the African Health Research Institute, South Africa

17%
Increase in peak infections of omicron in South Africa, compared with earlier delta wave

37%
Drop in peak hospitalisations when comparing South Africa's delta and omicron waves

76%
Drop in peak deaths when comparing South Africa's delta and omicron waves

protein in our bodies, causing the virus to release its contents inside a cell. With other SARS-CoV-2 variants, this cutting is done by a protein called TMPRSS2 found on the outside of cells, and it enables the viruses to then fuse with our cells.

With omicron, the spike protein doesn't seem to be cut while it is still outside our cells. Instead, the virus appears to first become enveloped by the membrane of a cell and pinched off into a small sac within that cell. Only then is the spike protein cut by proteins called cathepsins. This process is slower.

Put together with results from other teams, the finding suggests that omicron infects cells differently, making it more likely to infect the nose than the lungs. "The emerging picture is that this is probably the mechanism that underlies this switch from a lower respiratory tract infection to an upper respiratory tract infection," says Grove.

Why this has happened isn't known, he says, and there is no guarantee that future variants

will remain less severe. The 2006 SARS virus infected cells in the same way as omicron, yet oddly was far more deadly, says Grove.

"That said, as we all get immunity from vaccines and natural infection, our antibody and, importantly, our T-cell responses are being strengthened," he says. "So the ability of the virus to cause severe disease will be diminished."

However, the impact of a virus depends on how many people it infects as well as on how severe it is, which is why flu kills far more people than Ebola. In countries such as Australia that had previously succeeded in preventing large outbreaks, omicron is already having a much greater effect than other variants.

"This variant is much more infectious and spreading very rapidly," says Stewart. "It's already putting pressures on healthcare systems worldwide."

A big part of why omicron is so infectious is undoubtedly its ability to evade antibodies and infect a far greater proportion of people who have been vaccinated or infected by other variants. But this can't be the whole story.

One possibility is that it is related to the observed higher levels of the virus in saliva, meaning the variant is more likely to spread when people talk, shout, cough or sing.

"I think the higher levels of virus in saliva relative to previous variants must correlate in some way with the increased infectivity," says Diana Hardie at the University of Cape Town in South Africa. "I don't have proof of it, but it makes sense."

Her team has compared the results of PCR tests done using nasal and saliva swabs from the same individuals. The mouth swabs involved people coughing and then swabbing the inside of

Testing for the new variant

Omicron and changed rules have left people wondering what coronavirus test results really mean. **Clare Wilson** explains

both cheeks, above and below the tongue, on the gums and on the hard palate for at least 30 seconds.

With the delta variant, only 70 per cent of saliva swabs were positive when the nasal swabs were all positive. But with omicron, it was the other way round. Only 86 per cent of nasal swabs were positive when all the saliva swabs were positive.

In other words, saliva swabs may be a more reliable way of detecting omicron infections with PCR tests. Hardie thinks this applies to lateral flow tests – also known as rapid antigen tests – too, and plans to investigate this. There are already anecdotal reports that mouth or throat swabs are better than nasal swabs for detecting omicron.

Another reason why omicron is so infectious might be that a much higher proportion of people are asymptomatic and spread the virus without ever realising they are doing so. Lawrence Corey at the Fred Hutchinson Cancer Research Center in Seattle, Washington, and his colleagues have been analysing data from ongoing studies in South Africa where people have been tested regardless of symptoms.

The results suggest that the rate of asymptomatic infections is around eight times higher with omicron than with other variants, says Corey. The researchers think this could be a major factor in explaining why this variant is spreading so fast.

“It’s plausible,” says Stewart. But all these findings are preliminary and need to be confirmed, he says. “I think it’s very early days. Tread cautiously, I would say, in interpretations of everything.”

It makes sense that there would be more asymptomatic cases with omicron, says Grove. “That data is completely consistent with the idea that this virus is, on a person-by-person basis, less severe.” ■

How have covid-19 testing rules changed?

Many countries have lessened their restrictions for people with covid-19 since the start of the surge caused by the omicron variant. In the UK, the isolation period for people with an infection has been cut from 10 days to seven, as long as you get a negative result on two lateral flow tests (LFTs), also known as rapid antigen tests. These must be done on days six and seven, and carried out at least 24 hours apart. People should remain cautious around others and avoid those who are vulnerable, though.

“There’s huge variation in the length of infection and huge variations in viral load”

Could the isolation period be shortened further?

In the US, the isolation period has been cut to five days for people with no symptoms or whose symptoms are waning, although you should still wear a mask around others for five more days. The UK Health Security Agency (UKHSA) says it has no plans to follow suit, and that the situation differs in the two countries. In the UK, the isolation “clock” begins on the day of a positive test or the first day of symptoms, whichever is first. In the US, it starts on the first day of a positive test and, because these can take several days to access, “day five” is likely to fall later in the course of an infection.

Why do some people test positive even though they feel well?

Symptoms may not reflect how much virus is present in a person’s throat or nose. You

could have replicating virus but no symptoms and vice versa. “There’s huge variation in the length of infection, and huge variations in viral load,” says Al Edwards at the University of Reading, UK.

The UKHSA estimates that 10 to 30 per cent of people would still test positive on an LFT at day six, and that 5 per cent of people would still be positive at day 10, although the guidance in the UK says you no longer have to isolate on day 11, no matter what your LFT results show.

Can you test positive for covid-19 without being infectious?

Even if you have had three doses of vaccine, a positive LFT result means you are infectious to other people because virus protein is present in large quantities in your nose or throat. For that, the virus must be multiplying inside your cells.

However, PCR tests can give positive results for weeks after an infection, because they can detect tiny quantities of the virus’s genetic material, which aren’t necessarily infectious.

A positive lateral flow test suggests that the virus is replicating in your cells



GEORGE CLERK/GETTY IMAGES

In the UK, do I still need a PCR test if I have a positive LFT result?

People in the UK who test positive by LFT no longer need to take a follow-up PCR test, a temporary change. This is because background levels of covid-19 are so high – with about 1 in 15 people infected in the last week of December – that a positive LFT result is currently less likely to be false.

Does this mean people can just rely on LFTs now?

No. Anyone in the UK with covid-19 symptoms but a negative LFT result must still take a PCR test to rule out an infection. This is because LFTs have too high a rate of false negatives – saying you are free of covid-19 when you are really infected – to rely on them if you have symptoms. There are several reasons why LFTs are prone to false negatives, including people failing to swab their nose or throat properly and failing to mix the swab well with the testing fluid, says Edwards. “LFTs are only able to detect large amounts of virus.”

Are false negative LFT results more likely with omicron?

The UKHSA says initial studies suggest that LFTs are as sensitive to omicron as they are to the delta variant, although it is doing further tests. But the US Food and Drug Administration has said LFTs may be less sensitive at detecting omicron.

It is possible that LFTs that only involve swabbing the nose may be more likely to give false negative results for omicron, because this variant may be more likely to reach high levels in saliva before it does in nasal mucus (see “Understanding omicron”, left). ■